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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,237	BLOCK, ANDREAS	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. Claims 1-6, 8-12 are pending. Claims 7, 13-18 are canceled.

Claims 1-6, 8-12 are under consideration.

The Examiner inadvertently did not include claim 4, on page 4, line 1, wherein claims 1-3, 5, 7-12 were rejected under the 35 U.S.C. 103(a) as being unpatentable over Fitzsimons et al, in view of Nakagawa et al set forth in the Office action mailed 5/3/07. Therefore, claim 4 is included in the present office action as set forth below.

Claim Objections

Claims 4, 5, 6, 8, 9, 11, 12 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and cannot depend from any other multiple dependent claims. See MPEP § 608.01(n). However, in the interest of compact prosecution and customer service, and because said claims have been examined in the previous office action said claims are examined below.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim **1** rejection under 35 U.S.C. 102(a) as being anticipated by **Fitzismons et al,** (Gene Therapy, 8: 1675-1681, 2001) is **withdrawn**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-5, 8-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nakagawa et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001) in view of **Fitzsimons et al,** (Gene Therapy, 8: 1675-1681, 2001).

Nakagawa teaches a recombinant adenovirus vector, which contains a transgene encoding for IL-12 controlled by the tetracycline-regulated expression system (p 55, 2nd column, p 56 1st and 2nd column). Nakagawa teaches the utility of both two-component and one-component systems tetracycline-regulatable adenovirus vectors. Two component-systems utilize one adenovirus vector to express the transgene under the control of the TRE and a minimal promoter, and a second adenovirus vector to express the transactivator, either tTA or rTA, from a constitutive promoter (p 55, 2nd column, p 56 1st column, last paragraph). Furthermore, Nakagawa teaches a one component-system, wherein both expression cassettes are incorporated into a single adenovirus vector (p 55, 1st column, last paragraph and 2nd

column, 1st paragraph and reference by incorporation). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporated both expression cassettes into a single adenovirus vector, wherein the transgene is a nucleic acid sequence encoding the interleukin-12 transgene as claimed in the instant application, (claim 5). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the insert is inserted into the E1/E3-deleted backbone of Ad5 [reference by incorporation, (Corti et al, 1999), p 55, 2nd column, 1st sentence] as claimed in the instant application, (claim 8). Nakagawa also teaches that the tet-on system a "reverse" transacivator (rTA) with the opposite properties of tTA binds to the TRE and activates transcription only in the presence of tetracycline derivatives like doxocycline (p 54, 2nd column, last paragraph). Nakagawa teaches this tet adenovirus system provides new opportunities and improved safety for gene therapy applications in humans. Nakagawa teaches because systemic administration of IL-12 is toxic a regulated a temporal control and basal levels of the gene is essential (p 58). Nakagawa teaches by intratumoral injection of the vector in tumor bearing mice the hIL-12-medaited antitumor response was not compromised by reducing intratumoral IL-12 concentrations during later stages of the therapy (p 58 columns 1-2). Nakagawa differs from the present invention for not teaching the tet inducible cassette in the general structure as the claimed invention.

However, at the time of the instant invention **Fitzsimons** teaches a recombinant adeno-associated virus (rAAV) viral vector which contains an insert exhibiting the general structure in which, a) the $TetO_7$ is the heptamerized tetracycline operator; b) TK^+ is the minimal thymidine kinase promoter; c) tTA is a nucleic acid sequence which encodes a fusion protein from the repressor protein inducible by tetracycline and the transcriptional activation domain of the Herpes simplex virus VP16, d) CMV is the minimal cytomegalovirus promoter; e) the transgene

is a nucleic acid sequence which codes for a non-viral protein luciferase; f) intron[1] is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp; and g) intron[2] is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp (p 1675, 2nd column, last paragraph and p 1676, 1st column and figure 1) as is claimed in the instant case. **Fitzsimons** also teaches they have optimized the autoregulated-directional rAAV-based construct for in vitro and in vivo regulation of gene expression by doxocycline and they have demonstrated that rAAV-mediated transfer of reporter genes which can be regulated in vitro and in vivo with extremely low basal expression (p 1675, 1st column, 2nd paragraph). **Fitzsimons** also teaches they have minimized the size of the cassette and decreased the basal leakiness of the system, leading to tight regulation in the rat brain (abstract). **Fitzsimons** suggests the ideal regulatory system would be one in which all components were contained in one vector genome thus requiring a cell to be transduced with one vector rather than two or three (p 1679, 1st column, 2nd paragraph). **Fitzsimons** teaches that the bidirectional system was found to be appropriately expressed and regulated and used to transduce HEK 293 cells in vitro and the insulators may act more effectively in vivo to limit interactions between the ITRs and the expression cassette (p 1679, 2nd column). As such **Fitzsimons** provide sufficient motivation to apply the bidirectional tet-inducible cassette into the adenovirus of Nakagawa to tightly regulate IL-12 levels for gene therapy.

Accordingly, in view of the teachings of **Fitzsimons** et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the adenovirus vector of Nakagawa and insert the tetracycline-regulated cassette of **Fitzsimons** into the adenovirus for gene therapy with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification since Nakagawa teaches the temporal control and the basal levels of exogenous gene expression is

essential for IL-12 gene therapy and teaches efficacy and safety of tertracycline-regulated adenovirus-mediated IL-12 gene therapy for prostate cancer (p 58). Moreover, Nakagawa suggests that adenovirus vectors with tetracycline-regulated gene expression may prove useful not only for cytokine gene therapy applications, but also in other gene therapy applications, such as those of neurodegenerative diseases where, temporal control of exogenous gene expression is essential (p 58 under conclusion). One of ordinary skill in the art would have been particularly motivated to introduce the tet-regulated cassette of **Fitzsimons** into an adenovirus since **Fitzsimons** suggests the ideal regulatory system would be one in which all components were contained in one vector genome thus requiring a cell to be transduced with one vector rather than two or three and that the bidirectional system was found to be appropriately expressed and regulated in cells in vitro and the insulators may act more effectively in vivo to limit interactions between the ITRs and the expression cassette of the bidirectional tet-inducible cassette will tightly regulate IL-12 levels for gene therapy.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue that the references viewed alone or in combination, do not teach or suggest all of the elements of the rejected claims as the amended claim 1 is directed to an adenovirus vector and Fitzimons teaches a rAAV vector.

These arguments are not persuasive because **Fitzsimons** provides all the structural elements of the claimed vector in a rAAV vector (see figure 1, pBiG3r.5 construct, p 1676, 1st column). The structure of the claimed vector and that of **Fitzsimons** are the same with the exception in the case of **Fitzsimons** the bidirectional tet inducible cassette is inserted into a rAAV vector as compared to an adenovirus of the claimed invention. The combined cited

references of **Fitzsimons** and Nakagawa provides motivation to insert the claimed tet inducible cassette into an adenovirus by suggesting the tet adenovirus system provides new opportunities and improved safety for gene therapy. Nakagawa particularly provides motivation by teaching an immunotherapy model for prostate cancer with a tetracycline-regulated adenovirus vector expressing the cytokine IL-12. Moreover, Nakagawa teaches the efficacy of the tetracycline-regulated IL-12 gene expression in RM-1 cells and suggests that this adenovirus-based tTA tet system may be useful for regulated gene expression in broad range of mammalian cells and to create effective IL-12 vaccine and the adenovirus vector with tetracycline-regulated gene expression may prove useful not only for gene therapy of cancer but also for gene therapy applications such as those of neurodegenerative diseases where the temporal control of exogenous gene expression is essential. In addition, as discussed above **Fitzsimons** teaches that the bidirectional system was found to be appropriately expressed and regulated and used to transduce HEK 293 cells in vitro and the insulators may act more effectively in vivo to limit interactions between the ITRs and the expression cassette and as such **Fitzsimons** provide sufficient motivation to apply the bidirectional tet inducible cassette into the adenovirus of Nakagawa to tightly regulate IL-12 levels for gene therapy.

Nakagawa suggests that adenovirus vectors besides providing a highly efficient means of in vivo gene transfer, another advantage that adenovirus vectors have over many other viral vectors is flexibility in the choice of the promoter used to drive exogenous gene expression and this makes adenovirus vectors ideal for gene therapy applications where regulated transgene expression is sought. Nakagawa suggests that several "gene switches" have been developed by combining DNA-binding and transcriptional activation domains from bacterial, yeast, Drosophila and mammalian proteins to create hybrid transcription factors for achieving regulated transgene expression and these have included systems based on E. coli lacI

repressor protein (p 54, 2nd column, 2nd paragraph). Nakagawa suggests that regulatable systems based on E. coli tet operon offer a number of advantages compared to other expression systems for potential clinical use in the context of gene therapy. Nakagawa suggests that teaches because regulatory circuit not used by eukaryotic cells, transgene expression can be stringently controlled without affecting the expression of endogenous genes (p 54, 2nd column, 2nd paragraph). Therefore, the cited combined references provide all the elements of the claimed invention.

Applicants argue the claimed invention represents more than the predictable use of the elements described in the cited prior art as evidenced by the provided unexpected results as described below and by the publication of these unexpected results published by the Applicants in the provided reference of Block et al, (The Journal of Gene Medicine,. 2003). Applicants argue that **Fitzsimons** et al, Dox-regulated suppressibility (IL-12) not tested; Dox-regulated suppressibility (Luc): <204-fold; IL-12 expression (μg/24h/10^6 cells): not tested; tumor regression: not tested as compared to the vector of the invention Dox-regulated compressibility (IL-12): 6,000-fold; Dox-regulated suppressibility (Luc): 16,000-fold; IL-12 expression (μg/24h/10^6 cells): 1,000; tumor regression: almost completely. Applicants argue overall, the unexpectedly high expression as well as the surprising high doxocyclin-dependent suppressibility of the claimed vector constructs provide significant advantages regarding safety and efficiency when treating malignancies. Applicants argue the skilled person familiar with the cited references would not have been motivated to specifically modify the **Fitzsimons** reference to select the adenoviral vector system of the current invention.

These arguments are not persuasive because the tet inducible cassette construct of **Fitzismons** has the same structure as the tet inducible cassette construct of the claimed invention (see **Fitzsimons, p 1676, figure 1, construct pBiG3r.5).** The difference between the

Fitzismons, vector and the claimed vector is that the **Fitzsimons,** vector is a rAV vs the claimed adenovirus vector. However, upon the insertion of the **Fitzsimons** tet inducible cassette into the adenovirus cassette of Nakagawa inherently the end product of the combined cited references will produce the unexpected results of the claimed invention. The comparison between the **Fitzsimons** system and the vector of the invention does not provide lack of prima facie because lacks comparison between the vector of the combined cited references and the vector of the invention. The art of introducing DNA cassettes from a rAAV into an adenovirus is high and an ordinary artisan in the art of IL-12 gene therapy would have been sufficiently motivated to replace the rAAV with an adenovirus of the combined cited references. **Fitzsimons** and Nakagawa provides motivation to insert the claimed tet inducible cassette into an adenovirus by suggesting the tet adenovirus system provides new opportunities and improved safety for gene therapy. Nakagawa particularly provides motivation by teaching an immunotherapy model for prostate cancer with a tetracycline-regulated adenovirus vector expressing the cytokine IL-12. Moreover, Nakagawa teaches the efficacy of the tetracycline-regulated IL-12 gene expression in RM-1 cells and suggests that this adenovirus-based tTA tet system may be useful for regulated gene expression in broad range of mammalian cells and to create effective IL-12 vaccine and the adenovirus vector with tetracycline-regulated gene expression may prove useful not only for gene therapy of cancer but also for gene therapy applications such as those of neurodegenerative diseases where the temporal control of exogenous gene expression is essential.

Claim **6** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nakagawa et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001) in view of **Fitzsimons et**

al, (Gene Therapy, 8: 1675-1681, 2001) as applied to claims **1-5, 8-12** above, and further in view of **Lode et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001).

The 103 rejection of claims **1-5, 8-12** as being unpatentable over Nakagawa taken with **Fitzismons** is applied here as indicated above.

Nakagawa taken with **Fitzsimons** do not teach IL-12 is a single chain inteleukin-12.

However, at the time the invention was made, Lode is an exemplified prior art that teaches that it is routine or well-established in the art to employ a single chain IL-12 for protective immunity. Lode et al, teaches a single chain IL-12 fusion protein induces T cell dependent protective immunity in a syngeneic model of murine neuroblastoma. Lode teaches the single chain IL-12 fusion protein induces a T cell mediated immunity that completely protects mice from challenge with the wild type tumor cells as indicated by the complete absence of liver and bone marrow metastases in a novel syngeneic model of neuroblastoma (p 2475, 2nd column). Lode teaches the poor immunogenicity of this model clearly demonstrates the feasibility of efficient gene therapy with a single chain IL-12 fusion protein.

Thus, it would also have been obvious for one of ordinary skill in the art of IL-12 immunoengic composition to employ the single chain IL-12 of choice available in the art in the immunogenic composition of IL-12 of the combined cited references. One of ordinary skill in the art would have been motivated to employ the single chain IL-12 for gene therapy in order to demonstrate successful anti-tumor immunotherapy with a single chain IL-12 fusion protein that would facilitate clinical application of IL-12 gene therapy as suggested by Lode et al and particularly in view of the totality of the prior art at the time the invention was made. One of ordinary skill in the art would have been motivated to employ the single chain IL-12 since Lode et al have demonstrated that subcutaneous vaccination with IL-12 single chain fusion protein induces a T cell-mediated immunity that completely protects mice from challenge with wild type

tumor cells as indicated by the complete absence of liver and bone marrow metastasis in a syngeneic model of neuroblastoma (p 2475, 2nd column. 2nd paragraph).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue as claim 1 is amended to a recombinant vector an insert having the general structure tTA-intronI-TK+-TetO7-CMV+-intron2-transgene, wherein the vector is an **adenovirus. Fitzsimons** describes a recombinant adeno-associated virus (rAAV) viral vector, but does not teach or suggest an adenoviral vector as claimed in amended claim 1. This deficiency is not cured by the secondary reference by Lode et al. Applicants argue the unexpected results achieved with the presently claimed vectors are described in detail above. The secondary reference by Lode et al. does not add anything of significance except that the authors teach single-chain IL12 fusion protein.

These arguments are not persuasive because since **Fitzsimons** and Nakagawa provide motivation for an adenovirus tet inducible system as the claimed invention and since Lode teaches single chain IL-12 fusion protein induces T cell dependent protective immunity in a syngeneic murine neuroblastoma model and suggests the feasibility of efficient gene therapy with a single IL-12 fusion gene therefore, Lode et al, provide sufficient motivation for introducing the single chain IL-12 in a tet inducible system of an adenovirus containing the bicistronic cassette of Fitzsmons.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **2-4** rejection under 35 U.S.C. 112, second paragraph, as being indefinite or failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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